REMARKS

A. Status of the Claims

Claims 1-8, 10-51 and 53-55 are pending. Claims 12-41, 47-51, and 53-55 are withdrawn from consideration. Claims 1-8, 10-11 and 42-46 are rejected.

Claims 1-4, 6, 10, 42, and 44 are amended herein. No new matter is added by way of these amendments.

B. Rejections Under 35 U.S.C. § 112

Claims 1-8, 10-11 and 42-46 are rejected under 35 U.S.C. § 112, ¶ 1, as allegedly containing new matter. Applicants respectfully submit that withdrawal of this rejection is warranted in view of the amendments to claims 1 and 42, which were made without acquiescing to the Examiner's allegations and solely for the purpose of expediting prosecution.

Claims 42-46 are rejected under 35 U.S.C. § 112, ¶ 2 as allegedly indefinite. Applicants respectfully submit that withdrawal of these rejection is warranted in view of the amendments to claim 42, which were made without acquiescing to the Examiner's allegations and solely for the purpose of expediting prosecution.

On pages 6-7 of the Office Action the Examiner sets forth six claim rejections under 35 U.S.C. 112, ¶ 2, which are enumerated as paragraph (a)-(j). These claim rejections concern antecedent basis for the recited claim language.

Applicants respectfully submit that these rejections are inapposite in view of the claim amendments presented in the claim language that begins on page 2 of this paper. Accordingly, Applicants respectfully request reconsideration and withdrawal of these grounds of rejection.

C. Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 5, 6, 10, 11 and 42- 44 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Pre-Grant Publication No. 2001/0048929 to Chong et al. ("Chong") in view of an article by Wessels et al. in *PNAS 84*:9170-9174, 1987 ("Wessels (1987)"), Wang et al. in *PNAS* 95:6584-6589, 1998 ("Wang (1998)"), and Paoletti et al. in *Infect. Immun.* 62:3236-3243, 1994 ("Paoletti (1994)"). Claims 3 and 4 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), Paoletti (1994) and further in view of Paoletti (1999). Claims 7 and 45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), and Paoletti (1994) and further in view of Wessels (1995). Claims 8 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), Paoletti (1994) and Wessels (1995) in further view of Michon and Laude-Sharp.

Applicants respectfully traverse these rejections because it is improper to combine references where the references teach away from their combination. MPEP § 2145 (citing In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and alkali metal with the same beneficial result, combined with a reference expressly excluding antimony from, and adding iron to, a catalyst.)). Applicants respectfully assert that Chong teaches away from using capsular polysaccharides larger than 2 kDa to 5kD, and accordingly, also teaches away from combination with Wessels (1987).

According to the Office Action, Chong discloses a "multivalent immunogenic conjugate molecule comprising a carrier protein such as tetanus toxoid and multiple different purified carbohydrate fragments each linked to the carrier protein and a vaccine comprising the same in a physiologically acceptable carrier." Conceding that Chong does not identify multiple oligosaccharides of Group B Streptococcus to be at least three types such as types Ia, Ib, II and III GBS capsular oligosaccharides of molecular weight in the range of 80-120 kDa, the Office Action turns to Wessels (1987) for an alleged teaching of oligosaccharides of a GBS capsular polysaccharide having a molecular weight of 98,000 and their increased reactivity with or increased affinity for GBS type III antiserum.

Paoletti (1994) allegedly discloses different purified types Ia, Ib, II and III of Group B Streptococcus capsular polysaccharides and the concept of having, in a multivalent conjugate vaccine, said at least four different purified Group B Streptococcus capsular polysaccharides to elicit protective antibodies against the capsular polysaccharides, upon covalent linking to tetanus via 7-29% of the sialic acid residues oxidized [Office Action, page 9].

The Office Action asserts that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain 98,000 molecular weight oligosacchrides of Paoletti's (1994) purified types Ia, Ib, II and III of Group B Streptococcus capsular polysaccharides using Wang's method of ozone depolymerization and covalently link said oligosacchrides to the same tetanus toxoid carrier protein using Chong's novel glycoconjugate technology to produce the instant invention." [Office Action, page 9].

Independent claims 1 and 42 specify that "each polysaccharide of the at least three types of the purified bacterial caspular polysaccharides has a molecular weight in the range of 80 - 120 kDa." Applicants reiterate that none of Chong, Paoletti (1994), or Wang teach or

suggest bacterial capsular polysaccharides in this claimed molecular weight range. Further, Chong teaches away from using capsular polysaccharides in the range of 80 - 120 kDa. In particular, Chong states:

> Rationale for using oligosaccharides as antigens
> The minimum requirements for producing immunogenic glycoprotein conjugates are that the B-cell epitope(s) of the [capsular polysaccharides (CPs)] and the T-cell epitope(s) of the carrier are functional after covalent attachment. To randomly conjugate two or more CPs to the same carrier protein or T-cell epitope(s), the size of the carbohydrate is reduced to about 2 kDa to about 5 kDa to prevent steric hindrance effects. Chong, at ¶ [0060].

Chong expressly teaches away from using capsular polysaccharides larger than 2 kDa to 5 kDa since such large polysaccharides can cause steric hindrance during and/or after covalent attachment to the carrier. Accordingly, Chong does not make the present claims obvious. See, e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983) (holding claims not obvious in light of art that taught away from the claimed invention).

Applicant assert that in light of Chong, an ordinarily skilled artisan would not have a reasonable expectation of success for the combination as suggested by the Examiner. Whether the proposed combination has a reasonable expectation of success is determined at the time the invention was made. MPEP § 2143.03. As evidenced by Chong, at the time the invention was made, it was believed that conjugation of two or more capsular polysaccharides to the same carrier protein would result in steric hindrance if the two or more capsular polysaccharides were more than 2 kDa to 5 kDa. None of the art cited overcomes this deficiency, i.e., none of the references teaches or suggests that two or more capsular polysaccharide larger than 2 kDa to 5 kDa may be conjugated to the same carrier protein as without steric hindrance. Accordingly, an ordinarily skilled artisan would not have had a

reasonable expectation that combination of capsular polysaccharides with a molecular weight in the range of 80 - 120 kDa with a protein carrier would successfully result in the claimed multivalent conjugate molecules. MPEP § 2143 (stating a reasonable expectation of success is required to support a finding of obviousness). Therefore, it is respectfully submitted that the cited references do not provide a reasonable expectation of success in combining their teachings in the manner done by the Examiner.

Although not presently relied on by the Examiner, even U.S. Patent 5,811,102, cited in an IDS filed on July 18, 2005, and which states that an invention involving N-acyl derivatives of group B meningococcal polysaccharides "contemplates multivalent conjugates and their vaccines wherein different types of polysaccharides are conjugated to a single protein," Col. 5, lines 58, teaches away from Applicants' invention involving the larger sized polysaccharides by stating a preference for polysaccharides having an average molecular weight of 10,000 to 15,000 Daltons. Although polysaccharides in the region of 30,000 to 40,000 Daltons were also stated to be useful, such polysaccharides are still significantly smaller than those in the conjugates presently claimed by Applicants where steric hindrance would be expected to be of even greater concern.

Furthermore, Paoletti (1994) simply discloses a mixture of polysaccharides that may or may not be conjugated to a carrier protein and does not teach or suggest multivalent conjugate vaccines, or their use as claimed in the instant invention. Page 3238 of Paoletti (1994) states,

> GBS tetravalent conjugate vaccine was made by combining the same three individually prepared conjugates used in the trivalent GBS conjugate vaccine and the newly prepared Ib-TT vaccine. Stock solutions (1 mglml in PBS) of each conjugate (Ia-TT, Ib-TT, II-TT, and Ill-TT) were prepared, and equal volumes were combined and diluted with PBS to obtain a final concentration of 128 [Lg of GBS tetravalent conjugate vaccine per ml.

Paoletti's tetravalent conjugate is thus a mixture of individual conjugate molecules (Ia-TT, Ib-TT, II-TT, and Ill-TT) and not the multivalent conjugate of the present invention. The Applicants' invention is a multivalent conjugate molecule comprising a carrier protein covalently linked to at least three different types of purified bacterial capsular polysaccharides. The at least three different polysaccharides are all covalently linked to the same protein, unlike that disclosed in Paoletti (1994).

The polysaccharide/protein conjugate mixtures in Paoletti (1994) are physically different from the multivalent conjugate molecule described and claimed by Applicants. One of skill in the art reading Paoletti (1994) would therefore anticipate possible dissimilar immunogenic results when comparing the two, especially in light of this passage within Paoletti (1994),

> The results of our present studies demonstrate the induction of protective immunity to multiple serotypes of GBS by maternal vaccination of mice with a tetravalent GBS polysaccharide- protein conjugate vaccine. The individual capsular polysaccharides used in these studies were of various sizes and were oxidized to various degrees before coupling. As a result, the individual conjugates in the tetravalent vaccine differed in carbohydrate loading and in the degree of cross-linking of polysaccharide and protein. The influence of these physical properties on the immunogenicity of GBS conjugate vaccines has not been defined.

Applicant assert that in light of Paoletti (1994), an ordinarily skilled artisan would not have a reasonable expectation of success for the combination as suggested by the Examiner (MPEP § 2143 stating a reasonable expectation of success is required to support a finding of obviousness). Therefore, it is respectfully submitted that the cited references again do not provide a reasonable expectation of success in combining their teachings in the manner done by the Examiner.

It is respectfully submitted that the expectation of success of the combination has been provided by Applicants' claimed invention. The Examiner appears to have used impermissible hindsight reconstruction to pick and choose unrelated isolated teachings in the prior art to reject the claimed invention. In re Fritch, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992).

Claims 3 and 4 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), Paoletti (1994) and further in view of Paoletti (1999). The Examiner states that Paoletti (1999) discloses purified capsular polysaccharides of GBS types VI and VIII which, upon conjugation, induced protective antibodies and that these polysaccharide GBS types are important components of a multivalent GBS vaccine in particular regions [Office Action, page 10]. Again, the Applicants respectfully point out that Paoletti (1999), like Paoletti (1994), simply refers to a mixture of single polysaccharide-protein conjugate molecules and not the multivalent conjugate molecule of the present invention (see Materials and Methods in Paoletti 1999). The present invention provides a protein covalently linked to multiple different polysaccharides in a single molecule. Paoletti 1999 fails to teach or suggest a conjugate as claimed by Applicants. The fact that Paoletti over a five year period from Paoletti (1994) continued to mix monovalent conjugates to arrive at the "multivalent" conjugate is further evidence of the non-obviousness of Applicants' claimed invention. The Examiner states that the reference illustrates the use of five or six purified GBS capsular polysaccharides as recited in the Applicants' claims 3 and 4. Applicants respectfully argue that Chong, for the reasons stated previously, teaches away from such conjugates. As evidenced by Chong, at the time the invention was made, it was believed that conjugation of two or more capsular polysaccharides to the same carrier protein would result in steric hindrance if the two or more capsular polysaccharides were more than 2 kDa to 5 kDa. With the teachings of

Chong, one of the skill in the art would not be motivated to increase the number of polysaccharides used to five or six as this would likely increase the steric hinderance. The Applicants respectfully request withdrawal of this rejection.

Claims 7 and 45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), and Paoletti (1994) and further in view of Wessels (1995). The Examiner states that Wessels (1995) discloses the purified GBS V capsular polysaccharide and its use in a vaccine. Applicants respectfully argue that Chong, for the reasons stated previously, teaches away from such conjugates. As evidenced by Chong, at the time the invention was made, it was believed that conjugation of two or more capsular polysaccharides to the same carrier protein would result in steric hindrance if the two or more capsular polysaccharides were more than 2 kDa to 5 kDa. With the teachings of Chong, one of skill in the art would not be motivated to further include GBS type V when other GBS polysaccharides are already in use as this would likely increase the steric hinderance. The Applicants respectfully request withdrawal of this rejection.

Claims 8 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chong as modified by Wessels (1987), Wang (1998), Paoletti (1994) and Wessels (1995) in further view of Michon and Laude-Sharp. The Examiner states that the use of C beta protein as the carrier protein is referred to by Michon and Laude-Sharpe and combined with the other references, results in claims 8 and 46 as obvious over the prior art. The Applicants respectfully argue that Chong, for the reasons stated previously, teaches away from such conjugates. As evidenced by Chong, at the time the invention was made, it was believed that conjugation of two or more capsular polysaccharides to the same carrier protein would result in steric hindrance if the two or more capsular polysaccharides were more than 2 kDa to 5 kDa.

With the teachings of Chong, one of the skill in the art would not be motivated to produce the molecules of claims 8 and 46 since three capsular polysaccharides would be present in the final molecule. The Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment or credit any overpayment to Deposit Account No. 50-3732, Order No. 13564-105038US1.

Respectfully submitted,
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